REMARKS/ARGUMENTS

Claims 1, 9, 18, 19, 105-108 and 114-124 are active in this case.

Claims 118-124 are new and are supported on page 7, 1st paragraph, page 34, 2nd paragraph, pages 38-40 and pages 22-23 of the application as originally filed.

No new matter is added.

Applicants thank the Examiner for the courtesy of discussing the enablement rejection raised in the Official Action with their undersigned representative on January 21, 2009. During this discussion, it was emphasized that the specification provides sufficient basis to enable the claimed methods of treating traumatic brain injury (TBI) or improving neurological function in TBI as, for example, the specification describes how the discovered neuroprotective effect of G-CSF, for example shown in stroke models, is useful for the treatment of TBI. The specification on pages 38-40 also describes how such a method can be conducted with relevant parameters for assessing the improvement in neurological function.

It was further explained that the two main papers cited in the enablement rejection, Whalen 2000 and Sakowitz 2006, while reporting negative results after the administration of G-CSF to the test subjects, the negative results related to particular parameters such as edema volume and glutamate concentration. Indeed, a publication by Sheibani et al (also from the Whalen group) published in *Crit Care Med* (2004) vol. 32 (11):2274-2278, copy attached) actually assessed neurological function in mice models of TBI following G-CSF treatment. Sheibani et al conclude (page 2274, 3rd col., last para.): "The results suggest a beneficial effect of G-CSF on the pathogenesis of TBI.

Further details on these points are expanded upon in the discussion presented below.

The rejection outlined in the Official Action alleges a lack of enablement as the nature of using G-CSF to treat TBI is complex and unpredictable as evidenced by the art (Sakowitz-2006, Whalen-1999 and Whalen-2000), see Action at pages 6-7.

Specifically, citing Sakowitz et al, the rejection states that G-CSF failed to exert protective effects (Action at page 6 citing the Abstract). However, Sakowitz et al was not assessing neurological function but rather hemispheric water content and contusion volume (see page 141, FIGs 1 and 2) as well as glutamate concentrations (see page 141, Table 2). In fact, in the Introduction on page 139, col. 2, Sakowitz et al does acknowledge that G-CSF can be neuroprotective, just as described in the present application (see, e.g., specification at page 34, 2nd paragraph and page 7, 1st paragraph). However, as the mechanisms for the protection were not known, Sakowitz et al sought to assess whether the mechanism of G-CSF in TBI following a controlled cortical impact reduces brain edema and contusion volume. While the nature of his results indicate that the parameters they assessed were uneffected, this simply means that under the test conditions of Sakowitz et al, brain edema, contusion volume and glutamate concentrations were not apparent contributors to the neuroprotective effects provided by G-CSF. Sakowitz et al certainly does not conclude that G-CSF cannot act as a neuroprotective agent in TBI subjects and indeed rather acknowledges the neuroprotective effect as shown in the referenced prior studies.

Referencing Whalen 2000 at page 3716, col. 2, 2nd paragraph (page 6 of the Official Action), "functional outcome has not been assessed in this or any other study involving G-CSF administration in the setting of severe [TBI]." However, this does not mean that G-CSF cannot be used, as taught in the present application, rather that it had not been assessed. Further, the preceding sentence in Whalen-2000 is: "Another important limitation of the present study is that functional and histopathologic outcome were not measured"). Therefore, like Sakowitz et al, Whalen et al 2000 are simply assessing the effect of G-CSF on some mechanistic parameter and specifically neutrophil count (see Objective in the Abstract). The conclusions of Whalen 2000 are that pre-administered G-CSF did not stimulate neutrophils into the injured tissues and simply concluded a role for neutrophils in the pathogeneiss of

BBB damage but not brain edema (see the paragraph bridging col. 1 and 2 on page 3711). This similar assessment of parameters and mechanisms was the subject of the Whalen-1999 publication cited in the rejection on pages 6-7.

As already noted above, there is guidance for treating TBI with G-CSF in the specification (see, e.g., page 7, 1st paragraph, page 34, 2nd paragraph and page 38-40). These portions of the specification teach the treatment of a TBI with G-CSF including dose and time schedule. As discussed on pages 7 and 24, the inventors teach that TBI can be treated based on the data shown that G-CSF acts as a neuroprotectant, e.g., in stroke (see e.g. Examples 1, 6, 15, and 17).

Indeed, as noted in the meeting held on January 21, 2009, a second paper, Sheibani et al (also from the Whalen group, note that Dr. Whalen is the last named author) actually assessed the functional outcome and demonstrated a significant beneficial effect ("the results suggest a beneficial effect of G-CSF on the pathogenesis of TBI") Also, in Fig. 3, Sheibani et al measures spatial memory testing, e.g., a neurological function effected by TBI and showed a significant improvement in the subjects to which G-CSF was administered (see the paragraph bridging pages 2275 and 2276 "there was an overall improvement in performance in the G-CSF group compared with control group using the hidden platform ($P < .05$) as well as the visible platform. . ."). See also, Sheibani et al's discussion on page 2276, col. 3, 1st full paragraph).

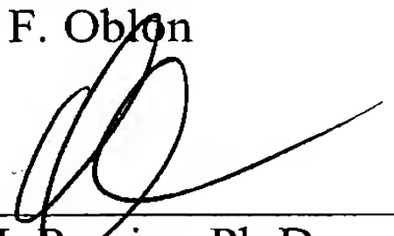
Thus, just as described in the present specification at least on the pages cited above, Sheibani et al confirms that which the inventors described, G-CSF acts as a neuroprotectant and can treat TBI, e.g., by improving the neurological function in the subject to which G-CSF is administered.

In view of the above discussion, reconsideration of the publications cited in the rejection and the publication attached, it is requested that the enablement rejection applied under 35 USC 112, first paragraph be withdrawn.

A Notice of Allowance is also requested.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.
Norman F. Oblon



Daniel J. Pereira, Ph.D.
Attorney of Record
Registration No. 45,518

Customer Number
22850

Tel: (703) 413-3000
Fax: (703) 413 -2220
(OSMMN 06/04)